Secondary updaten (ab 1990)
--> DHN
Faust Neskellen

PRIVILEGED & CONFIDENTIAL
ATTORNEY WORK PRODUCT

Covington & Burling Draft
May 20, 1992

SUMMARY OF DATA ON POTASSIUM CITRATE

Abstract. Potassium citrate is used as a flavor enhancer. It has been recognized as GRAS by the FDA for multiple uses in food.

Potassium citrate has been proposed as a cigarette coating or as an additive to cigarette paper. However, there is no information available concerning the pyrolysis of potassium citrate.

Potassium citrate is metabolized by the body much like citric acid. Excessive amounts of potassium citrate result in abnormal cardiac behavior in humans, as well as gastrointestinal discomfort. There were no significant treatment related effects in two chronic feeding studies using rats.

In subchronic studies, potassium citrate generally effected the growth rate of rats, but it does not appear to be mutagenic or teratogenic. Sodium citrate accelerated mortality in mice infected with tuberculosis.

I. Background. Potassium citrate ($C_6H_5K_3O_7$; CAS No. 00866-84-2), also known as the tripotassium salt of (citric acid) 2-hydroxy-propane-1,2,3-tri-carbonic acid, is a natural constituent and common metabolite of animals and plants. [Citric acid, 2-hydroxy-1,2,3-propanetricarboxylic acid and its salts are also natural constituents and common metabolites of animals and plants.] Citric acid is an intermediary compound in the Krebs cycle. In humans, the concentration of citrate is about 20 mg/l in whole blood, and 0.2-0.0 g of citrate is excreted daily in the urine (Ostberg, 1931; Sjöström, 1937). Citrate occurs in particularly high concentrations in fruits,

2029040977

including citrus fruits and their juices (Thunberg, 1953; Clements, 1964; Johnston and Hammill, 1968). Typical concentrations, fresh weight, are about 1 percent in orange juice and up to 8 percent in unripe lemon juice, as compared to 0.1 percent or less in peas, corn, cabbage, or human milk.

Potassium citrate is used as a food additive and therapeutic agent. In foods, it is used most frequently for pH control and as a flavor enhancer (GRAS list, 1972). The metal ion complexing properties of citrate make it useful as a sequestrant, antioxidant and preservative. For the age group 2 to 65+ years, the average intake of potassium citrate resulting from processed foods was calculated to be 280 mg/day (GRAS list, 1972). The level of addition was usually below 0.5 percent, expressed as a weighted mean. For the 0 to 5 month age group, the estimated average daily intake of added citrate is 560 mg.

Potassium citrate is used therapeutically as a diaphoretic and antipyretic in rheumatism, gout, bronchitis, and malaria. For these purposes, potassium is given in multiple daily doses of 1-2 g (Hagers Handbuch, 1976). Potassium citrate (10 mmol/l) also has been found to be useful in treating acidosis, diarrhea, and associated hypokalaemia (Islam, 1985; Meyer-Lehnert, 1991, because the citrate anion can be oxidized to CO_2 (Hagers Handbuch, 1976). Potassium citrate has been used in the oral treatment of nephrolithiasis (Lake and Brown, 1985; Pak et al., 1986 a to c; Buckalew, 1989), which can

2025040978

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

result from chronic hypocitraturia mediated by renal tubular acidosis, high intake of animal protein, or chronic diarrhea (Am. Pharm., 1984). Citrate helps prevent the formation of kidney stones through its ability to increase urinary pH by forming a complex with calcium. The chemical complex interferes with the urinary crystallization of calcium salts, reducing urinary saturation of calcium oxalate. Citrate also acts directly as an inhibitor of calcium phosphate and calcium oxalate crystal growth in the urine. Alkalinization increases the solubility of uric acid and reduces the formation of uric acid stones.

Potassium induced cardioplegia (intracoronary injection of a buffered, isotonic solution of potassium citrate containing 26 mEq. potassium/l) was shown to prolong the duration of cardiac tolerance to ischemia and to facilitate cardiac surgery (Effler et al., 1957; Lam et al., 1957; Sones, 1958; Gay and Ebert, 1973; Tyers et al., 1975).

Potassium citrate has been used to support sulfonamide therapy. It prevents crystalluria by alkalization of the urine (Hagers Handbuch, 1976). Potassium citrate also is used as gastric antacid (Merck Index, 1983) and to protect acid labile penicillin and other drugs against stomach acid (Hagers Handbuch, 1976). Potassium citrate has also been used therapeutically to assist persons in smoking cessation (Faust, 1976). In veterinary therapy, potassium citrate is used as a diuretic (Merck Index, 1983). The chemical also serves as a

2029040979

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

chelating agent for divalent cations in biological research and technology, e.g., 10 mmol PTC/1 can block the growth of cultured plant cells (Polacco, 1977). Other uses of potassium citrate include formulating photographic gelatin emulsions (Roempps, 1983), scrubbing sulfur dioxide from flue gases (Patent: Korosy), and electroplating with copper (Patent: Sumitomo Metal Mining Co., Ltd.).

The FDA has recognized potassium citrate as a GRAS substance (21 CFR § 182.1625 (1991)) for use as a sequestrant and multiple purpose food substance. FDA standards of identity provide for the addition of potassium citrate as an optional ingredient in certain cheeses [21 CFR § 133], ice cream [21 CFR § 135], jellies and preserves [21 CFR § 150], canned vegetables [21 CFR § 155, 156], and dressings [21 CFR § 169]. Food grade specifications for potassium citrate limit the concentrations of arsenic to 3 ppm and heavy metals (such as lead) to 10 ppm. The Select Committee on GRAS substances of the U.S. Life Sciences Research Office concluded in 1977 that, "[t]here is no evidence in the available information on potassium citrate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when used at levels that are now current or that might reasonably be expected in the future."

II. Use in Tobacco.

A. Function.

2029040980

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Potassium citrate has been proposed as a coating for cigarettes or additive to cigarette paper to produce a "self-extinguishing cigarette" (Patents: Mathews et al.; Guess; Reynolds). Information on the proposed amounts of the chemical required for these purposes is unavailable.

B. Use Level. An Industry maximum use level for potassium citrate has not been established.

III. Chemistry & Pyrolysis. Potassium citrate is synthesized from a concentrated solution of citric acid and potassium hydrogen carbonate. The dried product is crystallized from 60 percent ethanol (Hagers Handbuch, 1976) and appears as white crystals, granules or hygroscopic powder. The relative molecular mass of potassium citrate is 324.34, the density is 1.98, and the melting point is 230°C (pyrolysis). The solubility of potassium citrate is 1 g/0.65 ml in water, 1 g/2.5 ml in glycerol, and the chemical is practically insoluble in alcohol. The pH of potassium citrate is 8.5 in an aqueous solution. The chemical has no odor, a weakly basic/salty taste, and the monohydrate loses its water at 180°C.

Although unknown, it can be assumed that the fate of potassium citrate in a burning cigarette would be much like that of citric acid. Based on this assumption, and based on knowledge of the fate of citric acid in a burning cigarette, there are several conclusions that can be drawn concerning the

2029040981

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

pyrolysis of potassium citrate. First, the compound would decompose to potassium and citric acid in the cigarette, and most of the potassium would remain in the ash. Second, consideration of the chemical structure of α-hydroxy carboxylic acids as a general class indicates that the predominate chemical changes likely to occur upon heating are dehydration followed by decarboxylation (Furia, 1972).

Radioisotope studies conducted on chemically related acids such as malic, citric, and oxalic acids indicate that only 15 percent of the added organic acid transfers into the mainstream smoke. Of the material that transfers into the mainstream smoke, most is in the form of carbon dioxide, carbon monoxide, and other gases. Only about 3.5 percent of the added acids are transferred as solids (Newell, 1968).

Finally, it should be noted that lactic, malic, citric, oxalic, and other organic acids are natural constituents of tobacco, and collectively can comprise up to 9 percent of the leaf by weight. Therefore, use of these additives in tobacco cigarettes, at their currently used levels, would be expected to have a minimal impact on the chemical composition of smoke.

IV. Toxicology

A. Metabolism. Ingested potassium citrate dissociates into a potassium cation and a citrate anion under physiological conditions. Therefore, the metabolism of

2029040982

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

potassium citrate can be deduced from studies of citric acid metabolism. Orally administered citric acid is well absorbed and largely metabolized. Both exogenous and endogenous citric acid can be completely metabolized and serve as a source of energy, furnishing 2.47 Kcal/g. In animal studies, citric acid and sodium citrate were found to interfere with calcium absorption in vitamin D-deficient rats on a low phosphorus diet (Cramer et al., 1956). Citrates had an antirachitic effect in rats receiving an adequate phosphorus intake (Pileggi, 1956). Infants demonstrate efficient metabolism of citric acid and the kidney tubules reabsorb most (about 90 percent) of the filtered load of citric acid (Smith et al., 1940; Tischler et al., 1968).

B. Acute Human Toxicity. The most important human health consequence of excessive potassium intake and blood potassium levels (i.e., hyperkalemia, plasma potassium exceeding 5 mmol/l) is abnormal electric activity of the heart (Goodman and Gilman et al., 1990). Hyperkalemia can result from high oral or intravenous doses of potassium salts, or other potassium sources (e.g., acute or chronic acidosis). Cardiac toxicity associated with hyperkalemia is one of the leading causes of iatrogenic morbidity and mortality.

Premature infants fed a formula containing citric acid (680 mg/kg/day), developed metabolic acidosis without clinical signs when fed a high protein diet (3.19 g protein

20290409B3

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

per 100 ml formula), but not when fed a low protein diet (1.62 g protein per 100 ml formula) (Ballabriga et al., 1970).

No acute oral toxicity studies of citric acid in man have been reported. On the basis of the maximum tolerated chronic oral dose of citric acid in dogs and rabbits, Nazario (1952) estimated that an adult 70 kg man would be able to tolerate 53 g of citric acid daily without adverse health effects. However, there is one report that a young woman vomited and almost died after ingesting 25 g of citric acid in a single dose.

When a potassium citrate arrest was used during cardiac surgery, persistent ventricular fibrillation and depressed left ventricular function were observed (Nunn et al., 1959; Waldhausen et al., 1960). Cardiac arrhythmia also was observed in the elderly and patients with impaired renal function being treated with potassium citrate (Wilson and Farndon, 1982; Elizabeth and Carter, 1987).

Minimal side effects have been reported with potassium citrate therapy. The most common are gastrointestinal complaints, but these appear to be dependent on the dosage form (Pak et al., 1984).

A single dose of 10 g potassium citrate was reported to cause intestinal malabsorption of vitamin B_{12} (Palva et al., 1974). The impairment was frequent (30 percent) but mild, so that potassium citrate would be expected to cause a

20250040984

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

vitamin B_{12} deficiency only in persons already having marginal deficiency attributable to other causes.

In one 37-year-old man, who reportedly was allergic to several organic acids and had developed canker sores, headaches, general lassitude, and irritability from eating foods containing citric acid, direct application of potassium citrate crystals to the oral mucosa produced no effect (Tuft and Ettelson, 1956).

C. Chronic Animal Studies. Chronic toxicity studies involving citric acid have been performed on rats. In studies by Bonting (1952) and Bonting and Jansen (1956), three successive generations of albino Wistar rats were fed citric acid in the diet at concentrations of 0.15, 0.45, and 1.20 percent, providing an average intake of 100, 300 and 800 mg/kg/day, respectively. After a feeding period of up to 12 months, no adverse effects were observed in the treatment groups in growth, reproduction, mortality or blood components. The teeth were not harmed by the acid diets. Metabolic analyses of female rats found no abnormalities in nitrogen balance, mineral balance, acid-base balance or the gross and microscopic appearance of the tissues. On the other hand, the analysis found a decrease in ash and an increase in calcium content of the tibia, a slight increase in muscle calcium, a decrease in muscle sodium and total muscle phosphorus, and a decrease in liver sodium. The investigators did not consider

202904098S

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

these small changes in tissue composition to be evidence of adverse effects.

In a study by Horn et al. (1957), citric acid was fed to a group of 20 young male albino Carworth rats for 2 years at concentrations of 3 and 5 percent of the diet (average daily intake was 1.2 and 2.0 g/kg, respectively). Both experimental groups grew more slowly than the controls, but survival rates did not decrease. At the time of the sacrifice (2 years), there were no differences in the organ weights of the control and experimental groups. Results of microscopic examinations of the thyroid, lungs, heart, liver, spleen, kidneys, adrenal gland, stomach, small and large intestines, pancreas, bone marrow, and testes were within normal limits.

No published studies covering the carcinogenicity of potassium citrate or citrate were found.

D. Acute & Subchronic Animal Studies. The acute oral LD_{50} of citric acid (produced by Candida sp fermentation of normal paraffin) in mice was approximately 5 g/kg body weight and 12 g/kg body weight in rats (Yokotani et al., 1971). The signs of acute toxicity from orally administered citric acid in mice and rats were similar to those seen in organic acidosis and calcium deficiency. Animals given lethal doses of citric acid orally showed hemorrhaging of the gastric mucosa at necropsy.

2029040986

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Six young rats weighing about 75 g were fed a diet supplemented with 2.5 percent citric acid (about 2 g/kg body weight) for nine days (de Albuquerque and Henriques, 1970). The experimental group showed loss or no appreciable gain in weight during the first few days and then returned to the expected weight gain pattern.

Yokotani et al. (1971) fed groups of ten SD-JCL male rats (98-112 g body weight) citric acid (a refined product of yeast fermentation) for six weeks at 1.2, 2.4, and 4.8 percent of the diet; mean intakes of citric acid were 1.15, 2.26, and 4.67 g/ kg/day, respectively. Food intake decreased compared to the control group by 0.7, 2.6, and 4 percent, respectively. Growth rate was slightly reduced at all dose levels. The total plasma protein concentration was significantly less than that of the controls only at the 2.4 percent dietary level; slight decreases in blood cell counts and hemoglobin were not statistically significant. At the highest dietary level, plasma cholesterol concentration decreased, serum glutamic oxalacetic transaminase activity increased, the thymus weights were lower, and slight atrophy of the thymus and splenic follicles was found at necropsy.

Daily oral citric acid administration of 600 mg/kg (1.2 percent in the diet) to rats for more than 90 days produced no abnormalities in body weight gain, blood, histopathology of the viscera, or reproduction (Krop and Gold, 1945). Also, daily oral administration of citric acid to

2029040987

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

dogs, 1.38 g/kg, for 112-120 days was shown to produce no behavioral, biochemical, or histopathological abnormalities.

There are no available acute or subchronic animal studies for potassium citrate itself.

Information on dermal, subcutaneous, intravenous, or intraperitoneal acute toxicity was not found in the literature.

E. Genotoxicity & Mutagenicity. No evidence of potassium citrate mutagenicity has been reported in microbial assays involving S. cerevisiae D4 and S. typhimurium (strains TA1535, TA1537, TA1538), both with and without the addition of mammalian metabolic activation preparations (Litton Bionetics, Inc., 1975; ~~Litton Bionetics, Inc., 1975~~).

The genetic toxicity of potassium citrate has been evaluated in one Japanese study ~~in which DNA-damage was investigated~~, apparently using a cytogenic recombination assay. The results of the study are not readily accessible, because the publication is in Japanese (Ishizaki and Ueno, 1989).

F. Reproductive Toxicity & Teratology. Studies evaluating the teratological potential of citric acid in pregnant mice (≤ 241 mg/kg administered on days 6 through 15 of gestation), rats (≤ 295 mg/kg administered on days 6 through 15 of gestation), hamsters (≤ 272 mg/kg administered on days 6 through 10 of gestation), and rabbits (≤ 425 mg/kg administered on days 6 through 18 of gestation) found no

02290409B

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

adverse effects on nidation, maternal or fetal survival, or the number of abnormalities occurring in either soft or skeletal tissues. (Food and Drug Research Laboratories, Inc., 1973). In an evaluation conducted in the developing chicken embryo (Verrett, 1976), potassium citrate had no teratogenic effects.

In studies of chicken embryos performed by Landauer and Rhodes (1952) and Beaudoin (1968), citric acid was found to decrease the teratogenic effect of insulin and of trypan blue. Incubation of transplantable tumors (Walker carcinoma and Pliss lympho-sarcoma) in sodium citrate inhibited tumor growth at concentrations above 30 mg/kg (Prizhivoit, 1969).

G. Immunotoxicity. Fatal experimental tuberculosis progressed more rapidly in mice given a diet containing 8 to 10 percent sodium citrate (approximately 5.5 g/kg body weight) than in control mice (Dubos, 1955). Adding 2 percent to the drinking water also caused an accelerated rate of mortality in the animals. The investigator noted that addition of sodium citrate to the diets of control mice markedly reduced their rate of weight gain.

There are no available studies concerning the immunotoxicity of potassium citrate.

202940989

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

References

Am. Pharm. N.S. (1984), Orphan drug for kidney stones, 24: 22.

Buckalew, V.M. (1989), Nephrolithiasis in renal tubular acidosis, J. Urol., 141: 731-737.

Ballabriga, A., Conde, C., and Gallart-Catala A. (1970), Metabolic response of premature to milk formulas with different lactic acid isomers of citric acid, Helv. Paediatr. Acta, 25: 25-34.

Beaudoin, A.R. (1968), The effect of citric acid on the teratogenic action of Typan Blue, Life Sci., 7: 635-640.

Bonting, S.L. (1952), The effect of a prolonged intake of phosphoric and citric acids in rats, Thesis, University of Amsterdam.

Bonting, S.L. and Jansen, B.C.P. (1956), The effect of prolonged intake of phosphoric acid and citric acid in rats, Voeding, 17: 137-148.

Clements, R.L. (1964), Organic acids in citrus fruits. I. Varietal differences, J. Food Sci., 29: 276-280.

Cramer, J.W., Porrata-Doria, E.I., and Steenbock, H.A. (1956), Rachito-genic and growth-promoting effect of citrate, Arch. biochem. Biophys., 60: 58-63.

de Albuquerque, A. and Henriques, M.A. (1970), Ensaios sobre a toxi-cidade do acido ascorbico, Rev. Port. Farm, 20: 41-46.

Dubos, R.J. (1955), Effect of metabolic factors on the susceptibility of albino mice to experimental tuberculosis, J. Exp. Med., 101: 59-84.

Effler, D.B., Knight, H.F., and Groves, L.K. (1957), Elective cardiac arrest for open heart surgery, Surg. Gynecol. Obstet., 105: 407.

Elizabeth, J.E., Carter, N.J. (1987), Potassium citrate mixture: Smoothing but not harmless, Br. Med. J., 295: 293.

Faust, V. (1976), Raucherentwöhnuug - Nichtrauchertraining, Ther. de. Gegenw., 115: 1314-1326.

2029040990

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Food and Drug Research Laboratories, Inc. (1973), Teratogic evaluation of FDA 51-74 (citric acid) in mice, rats, hamsters, and rabbits, Reports prepared under DHEW contract no. FDA 71-260, Maspeth, NY.

Furia, T.E. (ed.) (1972), CRC Handbook of Food Additives, 2d edition, Cleveland, OH, The Chemical Rubber Co.

Gay, W.A., Ebert, A., Rail, T.W., Nies, A.S., Taylor, P. (eds.) (1990), The Pharamacological Basis of Therepeutics, New York: Pergamon Press, pp 697-704.

Subcommittee on Review of the GRAS List (Phase II), A comprehensive survey of industry on the use of food chemicals generally recognized as safe, Prepared under DHEW contract no. FDA 70-22 by the Committee on Food Protection, Division of Biology and Agriculture, National Research Council, National Academy of Sciences, Washington, D.C.

Guess, H.E. (1983), Smoking articles with reduced lateral threading of the smoke, patent: Brazil Pedido, BR 8300173 A, R. J. Reynolds Tobacco Company.

Hagers Handbach der pharmazeutischen Praxis (1976), Berlin, Springer Verlag, p 358-359.

Horn, H.J., Holland, E.G., Hazleton, L.W. (1957), Safety of adicip acid as compared with citric and tartaric acid, J. Agric. Food Chem., 5: 759-761.

Ishizaki, M. and Ueno, S. (1989), The DNA-damaging activity of natural and synthetic food additives, J. Food Hyg. Soc. Jpn., 30: 447-451.

Islam, M.R. (1985), Can potassium citrate replace sodium bicarbonate and potassium chloride of oral rehydration solution?, Arch. Dis. Child., 60: 852-855.

Johnston, F.B. and Hammill, M.M. (1968), The non-volatile organic acids of some fresh fruits and vegetables, Can. Inst. Food Technol. J., 1: 3-5.

Korosy, L.B. and Senatore, P.J. (1983), Flue gas desulfurization, patent: South Africa, ZA 8203698 A, Pfizer Inc.

Krop, S. and Gold, H. (1945), On the toxicity of hydroxyacetic acid after prologned administration: comparison with its sodium salt and citric and tartaric acids, J. Am. Pharm. Assoc. Sci. Ed., 34: 86-89.

2029040991

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Lake, K.D., Grown, D.C. (1985), New drug therapy for kidney stones: review of cellulose sodium phosphate, acetohydroxamic acid and potassium citrate, Drug Intell. Clin. Pharm., 19: 530-539.

Lam, C.R., Geoghegan, T., Sergeant, C.R., Geoghegan, T., and Sergeant, C.K. (1957), Experiences in the use of cardioplegia in the repair of interventricular septal defects, J. Thorac. Surg., 34: 509.

Landauer, W., Rhodes, M.B. (1952), Further observations on the teratogenic nature of insulin and its modification by supplementary treatment, J. Exp. Zool., 119: 221-261.

Litton Bionetics Inc. (1975), Mutagenic evaluation of compound FDA 75-4 (006100-05-6) potassium citrate, NF, FCC granular, Prepared for Food and Drug Administration under DHEW contract no [redacted].

Litton Bionetics Inc. (1975), Mutagenic evaluation of compound FDA 75-12 (006132-04-3) sodium citrate, USP, FCC hydrous, granular, Prepared for Food and Drug Administration under DHEW contract no [redacted].

Mathews, J.H., Durocher, D.F., and Hampl, V. (1985), Smoking article coating with decreased inclination for ignition and smoking articles, patent: German Offen. DE3429275 A1, Kimberly-Clark Corp.

The Merck Index (1983), Merck & Co., Inc., Rahway, NJ, p 1100.

Nazario, G. (1952), Agents acidulates utilizados em alimentos, Rev. Inst. Adolof Lutz, 2: 141-158.

Newell, M.P. and Best, F.W. (1968), The fate of oxalic, malic, and citric acids in the smoke of cigarettes, 22d TCRC, Paper #25.

Nunn, D.D., Belisle, C.A., and Lee, W.H. (1959), A comparative study of aortic occlusion alone and of potassium citrate arrest during cardiopulmonary bypass, Surgery, 45: 848.

Ostberg, O. (1931), Studien über die Zitronensäureausscheidung der Menschenniere in normalen und pathologischen Zuständen, Skand. Arch. Physiol., 62: 81-222.

Pak, C.Y.C., Skurla, C., Brinkley, L., and Sakhaee, K. (1984), Augmentation of renal citrate excertion by oral potassium citrate administration: time-course, dose frequency schedule, and dose response relationship, J. Clin. Pharmacol., 24: 19-26.

2029040992

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Pak, C.Y.C., Sakhaee, K., and Fuller, C. (1986a), Successful management of uric nephrolithiasis with potassium citrate, Kidney Int., 30: 422-428.

Pak, C.Y.C. and Peterson, R. (1986b), Successful treatment of hyperuricosuric calcium oxalate nephrolithiasis with potassium citrate, Arch. Inter. Med., 146: 863-867.

Pak, C.Y.C. and Fuller, C. (1986c), Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate, Ann. Intern. Med., 104: 32-37.

Palva, I.P., Salokannel, S.J., Palva, H.L.A., Rytkonen, U., and Timonen, T. (1974), Drug-induced malabsorption of vitamin B12, VII, Malabsorption of B12 during treatment with potassium citrate, Acta Med. Scand., 196: 525-526.

Pileggi, V.J., DeLuca, H.F., Cramer, J.W., and Steenbock, H. (1956), Citrate in the pevention of rickets in rats, Arch. Biochem. Biophys., 60: 52-57.

Polacco, J.C. (1977), Nitrogen metabolism in soybean tissue culture, Part 2: Urea utilization and urease synthesis require nickel ion, Plant Physiol., 59: 827-830.

Prizhivoit, G.N. (1969), O vliyanii limonnokislogo natriya na rost pervovaemykh opukkolei, Vopr. Onkol., 15: 77-83.

Roempps Chemie-Lexikon (1983), Stuttgart, Franckh'sche Verlagshandlung, p 2015.

Sjöström, P. (1937), Der Citrateghalt im Bluterum als Diagnosticum bei Krankheiten der Leber und der Gallenwege, Acts Chir Scand. Suppl., 49: 229.

Smith, A.H., Barnes, D.J., Meyers, C.E., Kaucher, M. (1940), The metabolism of citric acid by infants, J. Nutr., 20: 255-262.

Sones, F.M. (1958), Results of open heart surgery with elective cardiac arrest by potassium citrate in patients with congenial and acquired heart disease, Dis. Chest, 34: 299.

Sumitomo Metal Mining Co., Ltd. (1984), Copper plating baths, patent: Japan Kokai Tokkyo Koho, JP 84197587 A.

Thunberg, T. (1953), Occurrence and significance of citric acid in the animal organism, Physiol. Rev., 33: 1-12.

2029040993

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000

Tischler, V., Beno, P., Pavkovcekova, O., Lahita, I., and Jacina, J. (19xx), Oblicková clearance citrátu v dojcenskom veku, Cesk Pediatr., 23: 492-496.

Tuft, L. and Ettelson, L.N. (1956), Canker sores from allergy to weak organic acids (citric and acetic), J. Allergy, 27: 536-543.

Tyers, G.F.O., Todd, G.J., Niebauer, I.M., Manley, N.J. and Waldausen, J.A. (1975), The mechanism of myocardial damage following potassium citrate (Melrose) cardioplegia, Surgery, 78: 45-53.

Verrett, M.J. (1976), Investigation of the toxic and teratogenic effects of GRAS substances to the developing chicken embryo: potassium citrate, Food and Drug Administration, Washington, D.C., p 7.

Waldhausen, J.A., Braunwald, N.W., and Bloodwell, R.D. (1960), Left ventricular function following elective cardiac arrest, J. Thorac. Cardiovasc. Surg., 39: 799.

Wilson, R.G., Formation, J.R. (1982), Hyperkalemic cardiac arrhythmia caused by potassium citrate mixture, Br. Med. J., 284: 197-198.

Yokatani, H., Usui, T., Nakaguchi, T., Kanabayashi, M., Tanda, M., and Aramki, Y. (1971), Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats, J. Takeda Res. Lab., 30(1): 25-31.

20290409

Source: https://www.industrydocuments.ucsf.edu/docs/klvk0000